fibrosis and CD31 immunostaining for cardiac angiogenesis were performed. A $p<0.05$ was considered significant. Values were mean ± SE. LP was associated with heart hypertrophy ($p<0.05$ vs. NP) that was reversed 7-days PP (heart weight: NP=120 ± 3, LP= 163 ± 2, PP1= 145 ± 2, PP7= 117 ± 1 mg). Conversely, heart weight/body weight (hw/bw) ratio was decreased in LP ($p<0.05$ vs. NP) that was reversed in PP1 (hw/bw: NP=5.9 ± 0.1, LP= 4.5 ± 0.1, PP1= 5.6 ± 0.1). LV ejection fraction was reduced in LP ($p<0.05$ vs. NP) and was also restored at PP1 (NP=74 ± 4, LP= 57 ± 1, PP1= 73 ± 1%). Cardiac angiogenesis was significantly increased in LP ($p<0.001$ vs. NP), and was fully restored in PP7 ($p<0.001$ vs. LP) (Capillary density: NP=0.95 ± 0.01, LP=1.25 ± 0.02, PP7=0.98 ± 0.01 capillaries/myocyte). Similarly, VEGF was upregulated in LP, and was restored in PP7 (NP=1 ± 0.1, LP=1.4 ± 0.1, PP7=0.83 ± 0.1). There was no increase in cardiac fibrosis in pregnancy-induced heart hypertrophy. Transcript levels of extracellular matrix (ECM) degrading enzyme MMP2 were downregulated in LP ($p<0.05$ vs. NP) and were restored at 7-days PP (NP=1 ± 0.01, LP=0.47 ± 0.03, PP7=0.70 ± 0.1). In conclusion, pregnancy-induced heart hypertrophy is associated with increased cardiac angiogenesis, lack of fibrosis, decreased MMP2 and decreased diastolic function of the heart that are reversed postpartum. We speculate that physiologic heart hypertrophy of pregnancy has minimal cardiac ECM remodeling.

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Apolipoprotein-A1 Mimetic Peptide 4F Rescues Severe Pulmonary Hypertension in Rats and Inhibits Human Pulmonary Artery Smooth Muscle Cell Proliferation In Vitro

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Pulmonary hypertension (PH) is a characterized by arterial obstruction resulting from proliferation of pulmonary artery smooth muscle and endothelial cells. Genetic deletion of apolipoprotein-A1 increases airway hyperresponsiveness, inflammation, and collagen deposition in the lung. Apolipoprotein-A1 mimetic peptide 4F protects endothelial function, causes vasodilation, decreases inflammation and oxidative stress in lungs, yet its role in treating PH and right ventricular (RV) dysfunction is not known. We hypothesized that 4F may rescue pre-existing severe PH. We also investigate the effects of 4F on human pulmonary artery smooth muscle cell (hPASMC) proliferation in vitro as a possible mechanism of rescue by 4F. Twenty three rats were randomly divided into 4-groups. PH was induced by monocrotaline (MCT, 60mg/kg, s.c.). Severe PH was well-established at day-21 (PH, n=6) that progressed to RV failure (RVF, n=6) by day-30. One MCT-group was treated with 4F (50mg/kg/day, s.c., n=6) from day-21 to 30. Saline-treated rats served as control (CTRL, n=5). Serial echocardiography was performed to monitor cardiopulmonary hemodynamics. Cardiac catheterization was performed terminally to record RV-pressure (RVP). hPASMCs proliferation was assessed by MTT-assay. $p<0.05$ was considered significant. Values were mean ± SE. Rats developed severe PH 21-days after MCT (RVP=67.12 ± 1 vs. 29.8 ± 1 mmHg in CTRL, RV/LV+IVS= 0.65 ± 0.05 vs. 0.23 ± 0.02, RV-ejection fraction (RVEF)= 40 ± 1 vs. 65 ± 1%, all $p<0.05$ vs. CTRL), which progressed to RVF by day-30 [RVP=74 ± 1; RV/(LV+IVS)=0.68 ± 0.05; RVEF=28.6 ± 1%, $p<0.05$ for all vs. CTRL]. 4F-therapy from day-21 to 30 resulted in rescue of PH (RVP=47 ± 3 mmHg, RV/LV+IVS= 0.38 ± 0.02, RVEF= 51.7 ± 3%, $p<0.05$ vs. PH and RVF). 4F also inhibited hPASMC proliferation (~60% inhibition at 100ng 4F/ml medium, $p<0.05$). In conclusion, 4F rescues pre-existing severe PH and RV-dysfunction. Inhibition of PASMC proliferation may be one of the key mechanisms in this rescue.

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Genistein Therapy Reverses Lung Inflammation and Fibrosis during Severe Pulmonary Hypertension through Estrogen Receptor Beta

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Pulmonary Hypertension (PH) is a disease of increasing pulmonary arterial pressure characterized by extensive lung inflammation and fibrosis. We have previously shown that Genistein, a soy isoflavone, can rescue severe PH. Since Genistein is a selective Estrogen Receptor Beta agonist, here we examined whether Genistein can reverse fibrosis and inflammation induced by PH via an Estrogen Receptor Beta dependent mechanism. PH was established by treating male rats with monocrotaline (MCT, 60mg/kg, s.c.). At day 21 when severe PH was established, rats were treated with 10 day Genistein therapy (Gen group), Genistein therapy in the presence of selective Estrogen Receptor β antagonist PHTPP (Gen+PHTPP group), or were left untreated to develop right ventricular failure (RVF group). RVF animals developed severe pulmonary hypertension (RVP=72.96 ± 1.39mmHg vs 31.15 ± 0.56 mmHg in CTRL; RVEF=28.76 ± 0.79% vs 66.22 ± 1.40% in CTRL, all $p<.05$). Genistein therapy restored these abnormalities (RVEF=65.67 ± 1.08%, RVP = 43.34 ± 4.08 mmHg, $p<0.05$ vs RVF). Interestingly, in the presence of Estrogen Receptor Beta antagonist PHTPP, Genistein failed to rescue these animals (RVP=61.22 ± 4.40, RVEF=42.27 ± 2.7%, p=n.s. vs RVF). Masson's Trichrome staining revealed extensive lung fibrosis in RVF group, which was also restored with Gen therapy. Again, Gen+PHTPP group showed no reversal of pulmonary fibrosis. Immunoperoxidase staining showed an increase in ED-1 positive cells in the lung of RVF-group indicating increased inflammation. This change was reversed entirely by Genistein therapy. RT PCR also revealed that pro-inflammatory molecules TNFα and IL-1β were both elevated more than 2-fold in the lung of RVF animals and reversed with Genistein therapy (all $p<0.05$). Interestingly, Gen+PHTPP animals still showed significantly elevated ED-1 positive cells in the lung as well as elevated TNFα and IL1β (all p=n.s. vs RVF). These results suggest that genistein induced reversal of lung inflammation and fibrosis during pulmonary hypertension is mediated through Estrogen Receptor β.

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Estrogen Treatment Reverses Heart Failure-Induced Cardiac Fibrosis and Inflammation

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Heart failure is generally characterized by increased fibrosis and inflammation, which lead to functional and contractile defects. Recently we discovered that estrogen (E2) therapy can rescue advanced heart failure (HF) induced by pressure overload in mice by restoring left ventricular (LV) pressure and function. Here, we investigate the effects of E2 on reversing the adverse remodeling of the LV occurring during HF. Trans-aortic constriction procedure was used to induce HF. Once the ejection fraction reached ~30%, one group of mice was sacrificed and the other group was treated with E2 (30 μg/kg/day) for 10 days. In vitro, co-cultured neonatal rat ventricular myocytes and fibroblasts were treated with angiotensin II (AngII) in the presence or absence of E2. Quantitative real-time PCR showed that the transcript levels of the profibrotic markers collagen I, TGFβ, fibrosin 1 (FBRS) and lysil oxidase (LOX) were significantly upregulated in HF (from 1.00 ± 0.16 to 1.83 ± 0.11for collagen 1, 1.00 ± 0.86 to 4.33 ± 0.59 for TGFβ, 1.00 ± 0.52 to 3.61 ± 0.22 for FBRS and 1.00 ± 0.33 to 2.88 ± 0.32 for LOX) and were reduced with E2 treatment to levels similar to CTRL. In vitro studies validated our in vivo findings, as E2 also restored AngII-induced upregulation of LOX and TGFβ from 6.87 ± 0.26 in AngII to 2.80 ± 1.5 in AngII+E2 and 3.30 ± 0.25 to 1.59 ± 0.21 in AngII+E2, respectively (values normalized to CTRL). Furthermore, the pro-inflammatory interleukins IL-1β and IL-6 were upregulated from 1.00 ± 0.19 to 1.90 ± 0.09 and 1.00 ± 0.30 to 5.29 ± 0.77 in HF, respectively, and reversed to CTRL levels with E2 therapy. The anti-inflammatory interleukin IL-10 was downregulated from 1.00 ± 0.17 to 0.49 ± 0.03 in HF and reversed to 0.67 ± 0.09 with E2 treatment. This data strongly suggests that one of the mechanisms for the beneficial action of estrogen on left ventricular heart failure is through reversal of inflammation and fibrosis.

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Estrogen Directly Reverses Cardiac Remodeling Associated with Pulmonary Hypertension Induced Right Ventricular Failure

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Pulmonary hypertension (PH) leads to right-ventricular hypertrophy and failure (RVF). RVF involves adverse remodeling of the ventricular extracellular matrix (ECM). Recently we found that estrogen (E2) rescues PH-induced RVF. Here we explore whether the rapid restoration of RV function by E2 therapy during PH-induced RVF is in part due to a direct effect of E2 on the adverse ECM remodeling of the RV. In vivo, rats were injected with monocrotaline. At day 21, when PH had established, rats either received E2 (E2-group) for 10 days or were left untreated to develop RVF (RVF-group). In vitro, co-cultured neonatal rat ventricular myocytes and fibroblasts were treated with Angiotensin II in the presence or absence of E2 (AngII and AngII+E2 resp.). In vivo, E2 reversed RV fibrosis (4.06 ± 0.52% in CTRL, 33 ± 3.2 in RVF, 5.66 ± 0.33% in E2 group, all $P<.05$). In vitro, E2 similarly inhibited AngII induced increase in Collagen I transcript in cultured myocytes and fibroblasts (1.49 ± 0.04 in AngII, 0.75 ± 0.04 in AngII+E2, normalized to CTRL, $p<.05$). In vivo, E2 reversed PH induced increases of ECM remodeling enzymes OPN, ADAM15 and ADAM17 in the RV (9.33 ± 2.07 in RVF, 0.45 ± 0.16 in E2 for OPN; 2.13 ± 0.19 in RVF, 0.47 ± 0.07 in E2 for